

1 implications for access and reimbursement issues
2 although others noted that there is precedence for
3 off-label use in this field.

4 So, those are sort of the issues we
5 considered as a committee. Again, I would like to
6 go around the table and have people address what
7 indication they feel is appropriate given
8 everything we have said today.

9 I would like to start with Dr. Englund.

10 DR. ENGLUND: I would say for the second,
11 for the latter, for the treatment of HIV in
12 experienced patients.

13 DR. DeGRUTTOLA: Comments or just--

14 DR. GULICK: However you want. Certainly
15 comments are welcome.

16 DR. DeGRUTTOLA: I would say that what the
17 label should be depends on what we would really
18 want to feel has been demonstrated for the drug.
19 If the only requirement to have a recommendation
20 for treatment of HIV infection were that tenofovir
21 have activity in naive patients, my sense from
22 listening to most people was that the belief was
23 that it would have activity.

24 But if the reason for recommending the
25 broader indication was the belief that a treatment

1 that contained tenofovir was very likely to be
2 non-inferior to some other standard regimens that
3 are used, in other words, we could infer that the
4 tenofovir-containing regimen would be at least
5 non-inferior, there didn't seem to be a lot of
6 support or evidence for people being willing to
7 make that kind of claim, and unless there were
8 someone who believed that they could defend that
9 point of view, I would tend to recommend the
10 second, narrower indication, but would be
11 interested as we go around if there is anyone who
12 believes such a statement could be supported.

13 So, my vote at this point would be for the
14 treatment of HIV infection in patients who had
15 received prior therapy.

16 DR. GULICK: Let me just say we are not
17 actually taking a vote, but just so people know.
18 This isn't a formal vote, but I would like to hear
19 everyone's opinion around the table.

20 DR. WONG: I guess I would just reiterate
21 that I would not recommend making a more
22 restrictive indication in this case than we ever
23 have before, especially since the sponsor has
24 really done precisely what the HIV community and
25 also this committee has asked before, and that is

1 to specifically target treatment-experienced
2 patients.

3 It is biologically implausible to me that
4 an agent that has shown this degree of antiviral
5 effect in patients who are heavily pretreated would
6 not have at least that much effect in patients who
7 have not been pretreated, and therefore, I think
8 they should receive the same sort of approval that
9 every other HIV drug has.

10 DR. GULICK: Dr. Schapiro.

11 DR. SCHAPIRO: I would just like to repeat
12 one issue. It is not only the efficacy and the
13 safety. I think part of the safety, drug
14 interactions are important, and I do think that
15 regardless of the other large studies being done,
16 it would be relevant to see how it interacts with a
17 drug that is going to be given with.

18 That is a big part of the risk-benefit
19 ratio. We have had some discussions here at these
20 meetings. I think Gilead has done a wonderful job,
21 but I do think it is to be expected before allow
22 widespread use to see the interactions, and I think
23 some key interactions were not studied, and that is
24 part of the risk, as well.

25 It is not only are we confident it will

1 work, and I don't think that is too high a bar to
2 ask of companies. I also think we should know if
3 there is a PK difference in black women. I don't
4 think that is something which is too much.

5 I think that those are some of the studies
6 we should also see, and I think pending the results
7 of this study, the large study that is ongoing, and
8 some small PK studies, until we see that data,
9 then, I would say for now it is to be in
10 treatment-experienced.

11 DR. GULICK: Dr. Kumar.

12 DR. KUMAR: I agree 100 percent with what
13 Dr. Wong just articulated, that given everything
14 that was presented today, that it should not be a
15 restricted indication, but be approved for just the
16 treatment of HIV infection.

17 DR. GULICK: Dr. Hamilton.

18 DR. HAMILTON: I agree that it should be
19 given the broad approval with specific information
20 in the labeling that indicates where solid data
21 exists and where extrapolation has been allowed,
22 and hold Gilead's feet to the fire to deliver on
23 the remainder of the data that we need.

24 DR. GULICK: Dr. Yogev.

25 DR. YOGEV: I just carry one step further

1 your second comment before that we owe also the
2 public any relation to something which we did in
3 the past. Somehow my colleague failed to remember
4 that many times it did fail in the experienced
5 patient just because we did not indicate that we
6 want to see data. To me, to go the other direction
7 with the viral load, with the resistance, with the
8 interaction, I feel uncomfortable, and I think we
9 should reserve it to the population who really
10 needs it before we see too much resistance.

11 Therefore, I would suggest only for the
12 experienced patients.

13 DR. GULICK: Dr. Stanley.

14 DR. STANLEY: I, too, support only the
15 narrow approval for the experienced patients. This
16 is a whole new drug, and we don't yet know what
17 combinations it is going to be best in, but we do
18 know it is good in the treatment-experienced
19 patients that need another drug.

20 So, it is not a PI so you can use it like
21 the other PIs, you know, we haven't learned, we
22 haven't seen what those combinations are yet. The
23 other thing is that to me it really is irrelevant
24 what we did in the past, what we did five years
25 ago.

1 This isn't five years ago, it is today,
2 and we have more knowledge, we have more tools,
3 let's target this drug for now where it needs to
4 go, and as soon as we have got data that shows its
5 use as first-line therapy, I am happy to come back
6 and approve that.

7 DR. GULICK: Dr. Bone.

8 DR. BONE: Well, it would presumptuous of
9 me to have an opinion about this. It sounds like
10 there are some issues about how the regulatory
11 criteria for accelerated approval may have been
12 applied in the past as compared to the criteria for
13 traditional approval, and so on, but it just sounds
14 to me like it is beyond my scope to answer this
15 question.

16 DR. GULICK: We will count that as an
17 abstention then.

18 Dr. Wood.

19 DR. WOOD: I think the points raised by
20 Dr. Wong and Dr. Kumar are valid in terms of the
21 expectation that it is not unreasonable to expect
22 that treatment-naive patients would respond to this
23 drug, given the efficacy that has been demonstrated
24 in treatment-experienced patients, that naive
25 patients would respond.

1 However, the fact of the matter is, is
2 that we know that treatment-naive patients have
3 high viral loads. That is a fact. The other fact
4 is that we do not have efficacy data in terms of
5 the response of individuals with high viral loads
6 to this drug.

7 For that reason, I do not believe that it
8 is reasonable to extrapolate back to naive patients
9 that they will respond to the drug, because we have
10 no idea in terms of how efficacious this drug is in
11 individuals with higher viral loads.

12 So, I would recommend approval that is
13 restricted labeling.

14 DR. GULICK: Dr. Pomerantz.

15 DR. POMERANTZ: It remains a tough call,
16 but, Dr. Wong, I think that we are missing two data
17 sets, as I have said before, that I think Dr. Wood
18 is right, they are going to have higher viral loads
19 now in naive patients in most cohorts. If you
20 posit that this isn't going to work at very high
21 viral loads, which we haven't shown whether it is
22 or isn't in even the experienced, then, you are
23 adding a potential problem where one is not needed
24 to be added in 2001, and for those two reasons, I
25 vote for a more restrictive labeling.

1 DR. GULICK: Dr. Dorsky.

2 DR. DORSKY: I support the broader
3 indication.

4 DR. GULICK: Dr. Johnson.

5 DR. JOHNSON: I have heard everything that
6 everybody said, and I think two things. One, I
7 believe that it should get the broad indication. I
8 think, though, I am basically conservative, and it
9 should be restricted until we get the more complete
10 data sets. We are in the year 2001. I think we
11 need the data.

12 Can I just ask one more time, what is the
13 earliest that we could get the data set? Kim?

14 DR. STRUBLE: Gilead can answer that.

15 DR. JOHNSON: Gilead? I am asking Gilead,
16 if this is like it is available in two months?

17 DR. TOOLE: The last patient enrolled in
18 Study 903 will complete a 48-week visit in December
19 of this year. We are hoping to have something to
20 submit to the Agency late the first half of next
21 year, sometime in the May-June time frame.

22 DR. JOHNSON: So, Trip?

23 DR. GULICK: Which way are you going, Dr.
24 J?

25 [Laughter.]

1 DR. JOHNSON: I am going to go for the
2 broad indication because of biologic plausibility,
3 the resistance profile to me does not look like
4 this is an agent that is headed down the pathway
5 for a rapid resistance development, it is looking
6 ddI-like to me, and it is looking like another
7 active agent for treatment-naive, and I think we
8 will end up back, or Dr. Wong is, in about two
9 months.

10 DR. GULICK: Dr. Tebas.

11 DR. TEBAS: I agree that I suspect that is
12 what is going to happen, that biologically, it is
13 going to work in naive patients. The issue I think
14 with the label, as somebody pointed out before, is
15 not for physicians. People will use these drugs
16 however they want. It is for marketing. How this
17 drug is labeled is going to determine how this drug
18 is going to market.

19 If we have a broad indication, it will be
20 marketed for naive people. If we have a restricted
21 indication, the FDA is putting that restriction in
22 the company for a more narrow indication. That is
23 the decision that we are making here.

24 I think it makes perfect sense, this drug.
25 If somebody wants to take a bet, I think it is

1 going to work fine in naive people. When I see the
2 data, I am ready to--fortunately, I don't have to
3 give a vote, because I only have to talk here, but
4 if the FDA approves it for a broader indication, we
5 know that it is going to be marketed for naive
6 people, and I would like to see the data before
7 giving that vote, so I will restrict it, and as
8 soon as there is data, my vote would go to give a
9 broader indication.

10 I think once-a-day drugs are needed, and
11 this is the next big wave, is going to be
12 once-a-day regimens, and this drug could be
13 potentially very, very good for naive people. I
14 want to see the data.

15 DR. GULICK: Again, this isn't a formal
16 vote, so we will go to Dr. Munk.

17 DR. MUNK: I support the broader
18 indication based on the Agency's prior practices.
19 I would like to raise one potential risk, which is
20 that, kind of echoing something that Dr. Kumar
21 said, while some state ADAP programs and payers may
22 have no problem reimbursing off-label use, if, in
23 fact, the drug is given a more restricted
24 indication, that may deter some state ADAP programs
25 or other payers from adding the drug to their

1 formulary, and thereby make it less accessible to
2 the very patients we are trying to make it
3 accessible for.

4 DR. GULICK: Dr. Sun.

5 DR. SUN: At the risk of complicating the
6 discussion, can I ask a question about a possible
7 way out here?

8 [Laughter.]

9 DR. SUN: Is it possible to have a
10 relatively unrestricted indication statement, but
11 to have a caveat, just as we do for the part about
12 clinical efficacy, in other words, have a statement
13 that says there is currently no data in naive
14 patients?

15 DR. STRUBLE: Yes, I think that is one of
16 the approaches that we can take. The Agenerase
17 label actually has an indication for the treatment
18 of HIV infection, and there is a caveat there
19 saying that there is no data in PI-experienced
20 patients. So, that goes to the usage part of that,
21 and we can clearly work with that, too, you know,
22 put usage statements along with the indication.

23 DR. GULICK: Dr. Sun, do you want to plunk
24 your nickel down?

25 DR. SUN: That is where I am putting my

1 nickel.

2 DR. GULICK: That was a broad indication
3 with some caveats, is that what I heard? As Chair,
4 I can also express opinions here. I think that I
5 have every expectation, too, based on the data we
6 have seen, that this drug will work in naive
7 patients, but I am concerned that the risk-benefit
8 ratio may be different than experienced patients,
9 and I am uncomfortable based on the little data
10 that we have seen to agree with the broad
11 indication.

12 So, I would vote to restrict the
13 indication are present pending the results of
14 future studies.

15 For those of you who are keeping count on
16 this unofficial vote, we had 9 votes for limiting
17 it to the indication for treatment-experienced, 7
18 votes to recommend a broad indication, and we
19 excused Dr. Bone from voting.

20 And Dr. Lukert--oh, gosh.

21 DR. LUKERT: I am in the same position as
22 Dr. Bone. It is outside my area of expertise.

23 DR. GULICK: Perfect. Two abstentions. I
24 think this is clearly what it represents to the
25 Agency that the committee itself is nearly split on

1 this question.

2 DR. STRUBLE: I think we did get some
3 useful suggestions that we can craft an indication,
4 thank you.

5 DR. GULICK: Let's move to Question 2.
6 For the committee's benefit, Questions 2 and 3, we
7 are going to rely heavily on our outside experts
8 and members of the committee with particular
9 expertise in these areas. That is not to say
10 others can't make comments, but I am going to start
11 by referring to the experts in each of these fields
12 since they are rather narrow.

13 Question 2. Please provide your
14 assessment of the preclinical and clinical data
15 with regard to bone effects. Are there additional
16 nonclinical or clinical studies that the applicant
17 should conduct to further evaluate tenofovir-
18 associated bone abnormalities?

19 Dr. Bone, perhaps we could start with you.

20 DR. BONE: Thank you. I am sure Dr.
21 Lukert and I both appreciate the opportunity to
22 participate in this meeting, which in every other
23 respect is a little bit outside our usual area.

24 I think it is fair to say we have a clear
25 signal from the animal studies that there is a

1 potential for toxicity, and I don't think it is
2 resolved completely whether this is primarily a
3 renal effect, as may well be the case, with bone
4 consequences, or whether we have rigorously
5 excluded the possibility of a direct skeletal
6 effect, but I think the information we have
7 indicates there is an effect on mineral homeostasis
8 and that we have skeletal consequences. At least
9 that would be I think fair to say based on what we
10 have so far.

11 We have evidence that there is a problem.
12 There is an indication that this is not a severe
13 problem in the clinical trial as it potentially
14 might have been based on the animal studies.

15 The bone density data and fracture data
16 are only somewhat comforting because if we had seen
17 a problem based on the very limited short-term,
18 small number of patients, we would have really been
19 in trouble.

20 To give you an idea, we typically, in
21 order to detect a 50 percent difference in fracture
22 rate, we will have a trial of several thousand
23 subjects over several years for an osteoporosis
24 trial. So, the fact that we have not seen a
25 difference between the groups at this point is only

1 very limited as far as how comforting it is,
2 although it is certainly good that we haven't seen
3 anything more than we have.

4 The bone densitometry data that we have is
5 of interest, but as you heard from the discussion
6 with Professor Genant and myself, it doesn't really
7 address cortical bone as directly as some other
8 sites of examination would, and so there is more to
9 be done there, and that should be incorporated into
10 ongoing and future clinical trials.

11 I think there are a number of unresolved
12 questions that could be addressed actually, to a
13 certain extent, out of information that is probably
14 in freezers or potential information that is in
15 freezers.

16 It is at least somewhat unclear whether we
17 have thoroughly examined the question of whether
18 this is a renal effect on 1-alpha-hydroxylation.

19 I will just take a moment since we are
20 being asked to really address this. As Dr.
21 Teitelbaum pointed out, one of the important causes
22 of a mineralization defect is an insufficient level
23 of ambient mineral to mineralize the proteinaceous
24 matrix.

25 We do have one example at least or

1 actually more than one example of drugs that
2 directly affect mineralization, however, without
3 lowering the serum phosphorus, and detidronate is
4 an example of that, that is a drug that is actually
5 still on the market, but more likely in this case,
6 this is an effect on mineral homeostasis.

7 There could be an effect on GI absorption
8 and tubular reabsorption of phosphate as
9 postulated, that is a direct effect, and I think
10 this needs to be investigated further.

11 But some evidence was given that there was
12 a decreased level of 1,25-dihydroxy vitamin D, it
13 is 1-alpha-25-dihydroxy vitamin D.

14 Remember that the kidney is principally
15 responsible for the 1-alpha-hydroxylation of
16 vitamin D to its highly active form, and that this
17 is usually regulated by the serum phosphorus level
18 and, more importantly, in most clinical situations
19 by the parathyroid hormone level.

20 If the drug has an effect on the kidney
21 that inhibits 1-alpha-hydroxylation of vitamin D,
22 you would expect to see a rise in the parathyroid
23 hormone level as calcium absorption would be
24 impaired as a result of a lower 1,25-dihydroxy
25 vitamin D.

1 This is the phenomenon that we see in
2 patients with renal insufficiency of the usual
3 kind. Also, there is a feedback relationship
4 between the 1,25-dihydroxy vitamin D level and
5 parathyroid hormone secretion, so there is two
6 feedback loops.

7 The consequences of parathyroid hormone
8 going up include increased phosphate secretion, so
9 in the situation in which there is evidence of an
10 increased parathyroid hormone level, that may be at
11 least partly accounting for the phosphaturia and in
12 some cases drop in the phosphate level.

13 Now, I don't think that we can answer all
14 these questions today, but at least this is one of
15 the things that needs to be really exhaustively
16 pursued. It seems to me that from what I have been
17 hearing, that this is going to be a very important
18 drug for treatment of HIV, and it would be a pity
19 if we were unable to use it to its best effect
20 because we didn't fully understand this particular
21 consequence of using the drug.

22 The possibility of a subtle long-term
23 effect in adults is certainly something that needs
24 to be borne in mind, and it seems quite likely from
25 everything we have heard that if we understood the

1 mechanism well, we could probably monitor whatever
2 needs to be monitored with relatively simple,
3 relatively inexpensive, completely non-invasive
4 clinical tests, so that if some compensatory
5 mechanism like giving a little phosphate or
6 treating with one of the drugs that is
7 1-alpha-hydroxylated as a vitamin D analogue, could
8 be employed if needed, and it wouldn't even
9 necessarily mean the drug had to be interrupted if
10 we just understood what was the issue.

11 Another point here is that there is a
12 discussion about--and that is something, as we say,
13 that with long-term use and large numbers of
14 patients, something might emerge that we could head
15 off.

16 The other point is the use in pediatrics.
17 Growing bone is obviously much more vulnerable to
18 effects of abnormal mineralization. The pediatric
19 version of osteomalacia, for those who might not be
20 familiar, is rickets, and this is a situation in
21 which the bone isn't rigid enough to bear weight
22 without bowing, and it causes the other
23 consequences of rickets.

24 I don't mean to imply that this drug is
25 going to cause rickets in children, but I think

1 that it is important to understand the mechanism
2 before we get too far down that road, and to know
3 whether, for example, the dosing margin of safety
4 is adequate.

5 As I mentioned, I think that some of the
6 specimens in the freezers may actually help
7 elucidate this from even the completed trials, and
8 obviously, these are all considerations, many of
9 which have been taken into account in planning of
10 the ongoing and future trials.

11 I think there are two things that I would
12 suggest that can be studied both in animals and in
13 humans. One is sort of an intensive mineral
14 metabolism study which could be done in a subset of
15 the clinical trial population and also could be
16 done in experimental animals to look at calcium,
17 phosphorus and magnesium homeostasis absorption and
18 excretion, and the effects on parathyroid hormone
19 and the effects of parathyroid hormone in that
20 context.

21 I think, for example, tracers could be
22 used in animals that are affected in this way to
23 see if phosphate absorption really is impaired in
24 the gut, and there are a number of ways. I am not
25 the very best expert for that either, but that is

1 something that can be looked at to see if the
2 hypothesized defect in phosphate absorption is
3 really quantitatively important in this situation
4 or not.

5 I think that cortical bone monitoring, as
6 I mentioned earlier, might be more informative or
7 at least as imformative as some of the other sites.
8 I certainly wouldn't use it to their exclusion in
9 clinical trials, but if it did turn out that
10 cortical bone monitoring with a forearm measurement
11 were useful in clinical practice, that is less
12 expensive, easier, faster, and so on, than the
13 axial bone density measurement. It might be a
14 great advantage.

15 I think that is very important that all of
16 these measurements could be studied in clinical
17 trials including let's say more extensive
18 monitoring of excretion rates of the various
19 minerals I mentioned.

20 I am sure Dr. Lukert will have a lot to
21 add.

22 DR. GULICK: Dr. Lukert, if you can hear
23 us?

24 DR. LUKERT: Yes, thank you. I certainly
25 agree with everything that Dr. Bone said. I am not

1 very comforted by the lack of change in bone
2 density measurement because bone density isn't a
3 sensitive marker for bone changes in osteomalacia
4 like it is for osteoporosis, and we certainly have
5 to look at it over a long period of time and even
6 over a long period of time you may not see the fall
7 in bone density of patients with osteomalacia.

8 I also believe that we have a great need
9 for some histomorphometric studies, because if we
10 had histomorphometry in the monkeys that had--

11 DR. GULICK: I am sorry, you are fading in
12 and out on us.

13 DR. LUKERT: [Inaudible.] I would be more
14 reassured if we didn't see osteomalacia in that
15 group.

16 DR. GULICK: I am sorry. Could you repeat
17 your last point, because I think we missed it?

18 DR. LUKERT: I am sorry. Can you hear
19 what I am saying?

20 DR. GULICK: I can now, but you are kind
21 of fading in and out.

22 DR. LUKERT: What I am saying, if we had
23 bone histomorphometry on these monkeys, who were on
24 doses of the drug four times those of humans, then,
25 I would be much more comforted if we didn't see

1 osteomalacia in that group.

2 I think that we don't know anything about
3 even histology at that higher dose. It makes it
4 difficult to say you actually see osteomalacia in
5 the human dosage.

6 I agree with Dr. Bone that we desperately
7 need 1,25-dihydroxy D levels, and we need to know
8 whether this is a direct effect on bone or mediated
9 through phosphates, and that is why I think the
10 bone histomorphometry is extremely important.

11 The problem is that osteomalacia is such
12 an indolent, smoldering problem that you can see
13 severe bone problems before you see the fall in the
14 serum phosphorus or the rising up of phosphatase.

15 They are all problems that can be dealt
16 with, but I think they have to be addressed.

17 DR. GULICK: Any other comments, Dr.
18 Lukert?

19 DR. LUKERT: I think at this point that we
20 really don't have a good idea at all what the
21 toxicity is of bone at the doses that are being
22 used in humans. I really think we have to settle
23 that problem.

24 DR. GULICK: Thank you. Dr. Bone?

25 DR. BONE: I was just going to ask Dr.

1 Lukert what she thinks about studies in children at
2 this point.

3 DR. LUKERT: I think I would be opposed to
4 studies in children until we see what the effects
5 in adults are. Just as you pointed out, children's
6 bones are so much more susceptible to any of these
7 adverse effects.

8 DR. GULICK: Dr. Struble or Murray?
9 Sorry.

10 DR. MURRAY: I just want to say that when
11 the expanded access program opened up, we have
12 gotten numerous requests for children. Children
13 typically in the United States have had lots of
14 drugs, and they need drugs or they will die of
15 AIDS, which is unacceptable, and I think that there
16 is probably a tradeoff where the possibility of
17 maybe some bone toxicity or succumbing to their
18 disease, that can be dealt with.

19 When it is approved, it will be used in
20 children. If we don't study children and find out
21 what dose is appropriate and what dose is similar
22 to adults, then, it might be likely that children
23 will get higher doses, putting them at more risk
24 for bone toxicity.

25 So, I don't think that there is any way

1 that we cannot proceed with careful studies in
2 children. It is going to start with the NCI. It
3 will be a reality. We need this drug for adults.
4 It will be used in children. We have already had
5 to give exceptions for expanded access in children.

6 At first, I was one of the proponents of
7 saying withhold in children, but then when expanded
8 access opened up, I knew that the cat was already
9 out of the bag, and I think it is something we have
10 to deal with.

11 DR. GULICK: Dr. Englund, a follow-up
12 comment?

13 DR. ENGLUND: I would just like to say as
14 a pediatrician we absolutely, definitely need some
15 salvage protocol drugs for our kids who are aging
16 into the teenage years and are resistant to
17 everything. That is number one.

18 Number two, I think we could turn this
19 question around and we might be able to get an
20 answer out of children before you get it out of
21 adults, so we could use this in a controlled manner
22 to do the studies, not the bone biopsies, but
23 measuring the vitamin levels and the phosphorus,
24 and we can get 24-hour clearances and things like
25 that.

1 I think that maybe we could even get an
2 answer out of growing children faster than we could
3 out of adults anyway, so I would propose that it be
4 used under a study situation, but we need to get
5 the answer.

6 DR. GULICK: Dr. Bone, a follow-up
7 comment?

8 DR. BONE: I take your point about the
9 urgency of treating, and I am sure Dr. Lukert does,
10 too, about the urgency of treating the children
11 with this disease. I think that you will find that
12 the balanced studies and homeostatic studies are
13 not as easy in growing children because they tend
14 to be in positive mineral balance, and it is hard
15 to predict by how much an individual, and
16 particularly in a sick child.

17 What I think this does, then, is sharply
18 focus the point that everything needs to be done to
19 get all the information possible from prior studies
20 and from animal studies, and the rather vague
21 response that we have as far as what is really
22 available in the way of information about vitamin D
23 metabolites, and so forth, just must be focused
24 very sharply and immediately, but I really think
25 that that information can be extracted if the

1 samples still exist.

2 The response that I got to the question
3 about that was that we didn't have adequate
4 baseline samples, but this was from a controlled
5 study where there was a placebo group in animals
6 and also in humans.

7 So, it seems to me that while it is always
8 nice to have a baseline group, if you have a good
9 control, it may not be fatal to not have good
10 baseline data, and this just has to be extremely
11 high in priority, and I, while quite taking the
12 point that the urgency of treating children is
13 great, I think neither Dr. Lukert nor I were
14 suggesting that we should not treat children. I
15 think what we are saying is you had better figure
16 this out before you get very far down that road,
17 and that means get busy.

18 DR. GULICK: Dr. Tebas.

19 DR. TEBAS: First, I want to say a caveat.
20 I am not by any means an expert in bone disease. I
21 am a physician that happened to make an
22 observation.

23 I think what is needed in this regard is
24 longer and larger trials, and I think 903 is a good
25 trial. I suppose it will also give the opportunity

1 to find patients with--if something is going to
2 happen, those patients that develop the problem
3 with the most severe phenotype could have a bone
4 biopsy, and those patients would provide a lot of
5 information to the bone experts to figure out what
6 is exact effect of this drug, if it has an effect
7 on bone metabolism in adults.

8 So, I think 903 is a good opportunity, and
9 if somebody, and if the company sees somebody
10 developing an unusual phenotype, those biopsies
11 should be pursued to try to obtain the maximum
12 information from those patients and not going back
13 later on to try to obtain that data.

14 DR. BONE: I think as Dr. Lukert pointed
15 out a moment ago, that biopsies would probably show
16 an abnormality before the phenotype was expressed
17 clinically or by laboratory results. Would you
18 agree, Barbara?

19 DR. LUKERT: Yes, I would. I just think
20 that testing is critical. We could use it rather
21 quickly.

22 DR. BONE: The mineral homeostasis study
23 should be very short term.

24 DR. GULICK: Dr. Yogev.

25 DR. YOGEV: Obviously, I am not a bone

1 expert at all, but just one observation. I thought
2 that the newborn, the way it grows is different
3 than adolescent, different than at 6, 7 years of
4 age. The reason I mention it, I am a little bit
5 concerned that the study in pediatrics go from 6
6 months to 17 years of age, and from my experience
7 in the past, there are drugs who are approved, for
8 example, from 6 months on with three kids or four
9 kids below the age of 2 years, and I think the bone
10 in that population is so different, and especially
11 in the newborn, I don't understand why we stop at 6
12 months, we don't go to the younger population,
13 especially we are seeing more and more resistance.

14 So, this one point, that studies in
15 children should be devised better with a bone
16 expert, do we need to separate to a different
17 group. The other point is many of those studies
18 are done in Europe and in United States, and those
19 children from the bone mineral, the vitamin D are
20 different than the people in developing countries,
21 that a high percentage of them are vitamin D
22 deficiency, have other problems, that we need to
23 put caveat to that, that we need to see studies in
24 this unique population already has the bone
25 potential impairment because those drugs should be

1 also aimed to the 10 million kids at this point who
2 are HIV infected.

3 DR. GULICK: Dr. Tebas, a follow-up
4 comment?

5 DR. TEBAS: Dr. Bone, you are the expert.
6 Would you suggest doing a bone histomorphometry
7 study in a selective group of patients that don't
8 have like with tetracycline labeling and after
9 being exposed to these drugs for a long time, to
10 study mineralization to see if there is an issue or
11 not?

12 DR. BONE: Well, there may be some issues
13 related to the biopsies, but this is something that
14 we do for every drug we study for osteoporosis, and
15 even in those cases, those are drugs that have been
16 very thoroughly studies preclinically. I think the
17 first question is what is going on in the monkeys
18 at moderate exposure dose, a 4-fold exposure.

19 Maybe Dr. Lukert would also have an
20 opinion about biopsies in patients who are not
21 necessarily symptomatic, but in adults.

22 DR. LUKERT: Yes. I really would like the
23 issue addressed to the monkeys, because I think it
24 might really settle some questions. If those were
25 normal at doses 4 times what are used in humans, I

1 wouldn't be so concerned, but I think that maybe
2 you could pick the subgroup of people who did have
3 any subtle biochemical abnormalities like the
4 people who become hypophosphatemic, and biopsy
5 those people.

6 Certainly, if those people were absolutely
7 normal, I think you could put some of these
8 concerns to rest.

9 DR. GULICK: Dr. Munk.

10 DR. MUNK: I am kind of growing
11 increasingly concerned as this discussion proceeds,
12 and I believe it was Dr. Lukert's term that
13 osteomalacia would be a smoldering problem, and
14 unfortunately, people living with HIV and taking
15 anti-HIV medications are subjected to an ever
16 lengthening list of smoldering problems, so I would
17 strongly urge the sponsor to figure out, if
18 possible, the best way to get an early read on
19 whether or not this problem is occurring, and to
20 maintain follow up of a large number of patients
21 for a very long period of time to monitor the
22 extent of the problem.

23 DR. GULICK: Yes, Dr. Goldberger or Dr.
24 Birnkrant, either one.

25 DR. BIRNKRANT: I was wondering if you

1 could recommend, though, at this point, a standard
2 battery of testing and how often these tests should
3 be performed in patients receiving tenofovir DF.

4 DR. BONE: You are talking about not study
5 patients, but patients in clinical practice?

6 DR. LUKERT: I would say every three to
7 four months, because that is sort of in sync with a
8 bone remodeling cycle, probably looking
9 particularly at the phosphorus and the parathyroid
10 hormone levels and the calcium.

11 In the beginning, the 1,25-dihydroxy D
12 levels until we know what is going to happen to
13 those. Of course, we are going to assume that we
14 would have 25-dihydroxy D levels on all of these
15 patients to make sure that we aren't dealing with a
16 vitamin D deficiency.

17 DR. GULICK: Dr. Bone, I am not sure
18 everyone in the room heard that, if you want to
19 repeat.

20 DR. BONE: Well, I agree with Dr. Lukert
21 that we would want to, at intervals of about three
22 to four months, measure the serum calcium,
23 phosphorus, and alkaline phosphatase levels. I
24 think we would probably want to measure the bone
25 specific alkaline phosphatase level because there

1 are apt to be other reasons, not the least of which
2 would be hepatitis, that would alter the total
3 serum alkaline phosphatase level, and might be
4 confounders.

5 We would want to measure the intact
6 parathyroid hormone level, 25-hydroxy vitamin D,
7 and 1,25-dihydroxy vitamin D at baseline to make
8 sure that we didn't have a baseline abnormality.
9 25-hydroxy vitamin D is the best measure of the
10 adequacy of vitamin D nutrition, and we usually
11 find that levels of around 30 nanograms per mL or
12 higher are associated with a good vitamin D status,
13 lower levels which fall within the normal range for
14 the laboratory may still be suboptimal.

15 The 1,25-dihydroxy vitamin D is an issue
16 that has been raised here, and there is a
17 possibility that its production is impaired, and
18 that would presumably have a reciprocal
19 relationship with the parathyroid hormone level.

20 I would agree with those recommendations.
21 I think a baseline bone density measurement
22 including the forearm is probably reasonable
23 because you are obviously going to be more
24 concerned about patients who have low bone
25 densities, but as Dr. Lukert has pointed out, the

1 central bone density is a very poor way of
2 detecting this problem and were not very sensitive.

3 I think another pretty obvious thing to do
4 is to make sure that the patient's calcium and
5 vitamin D intake is adequate according to general
6 recommendations, because it would be ridiculous to
7 impose a very well-known problem on this obscure
8 one by not making sure that everybody had
9 sufficient calcium and vitamin D intake. That is
10 only a couple of pills, but it is something to take
11 into account.

12 DR. GULICK: Dr. Pomerantz, the last word.

13 DR. POMERANTZ: No, no, it is not going to
14 be the last word. I was going to ask Dr. Bone to
15 have the last word, because I am a little confused
16 with that.

17 Upfront, what are you going to get on
18 these patients, what would you recommend, the exact
19 tests that you would get when they come in, before
20 they start on the drug?

21 DR. BONE: If you send me a patient and
22 said you have a patient you were planning to start
23 on this drug--

24 DR. POMERANTZ: Precisely.

25 DR. BONE: --I would get just what I just

1 listed.

2 DR. POMERANTZ: Do you want to list them
3 again for me?

4 [Laughter.]

5 DR. BONE: Okay. Barbara, please chime
6 in. I may add one or two things. I think we would
7 get a serum chemistry panel that included calcium,
8 phosphorus, and alkaline phosphatase level. I
9 would add probably a bone-specific alkaline
10 phosphatase level.

11 We would measure the baseline 25-hydroxy
12 vitamin D level to make sure the patient was
13 vitamin D sufficient before starting therapy. It
14 is easy to fix if they are not, but you wouldn't
15 want to initiate the therapy until you were sure
16 that they--at the very least, you can just give a
17 vitamin D injection that is good for several
18 months. There is a depo injection.

19 We would get the parathyroid hormone level
20 and 1,25-dihydroxy vitamin D levels to make sure
21 they were all right to begin with. It would make a
22 lot of sense to get a baseline 24-hour urine
23 collection for calcium, phosphorus, creatinine, and
24 sodium.

25 What we are doing here is the equivalent

1 of a clinical trial, because we don't have the
2 clinical trial data. This is the kind of
3 information you might very well not need later on.

4 DR. POMERANTZ: You would do this on every
5 patient that we start this drug on?

6 DR. BONE: Well, if you send me a patient
7 and said you wanted to have their risk of
8 osteomalacia characterized and me to help you
9 monitor them, that is what I would do.

10 If we don't get this information, then,
11 you won't know what is going on.

12 DR. POMERANTZ: So, you have these seven
13 things upfront.

14 DR. BONE: Right, and I think there is an
15 argument to be made for a bone mineral density
16 measurement, as well. I don't know that that is
17 absolutely essential for the reasons that Dr.
18 Lukert mentioned, but there is a case to be made
19 for them. I wasn't asked to come to this meeting
20 with this exact set of recommendations for clinical
21 practice, but that is what Dr. Lukert said pretty
22 much.

23 DR. POMERANTZ: All right. That is
24 upfront. If you don't mind, Trip.

25 DR. GULICK: Go ahead.

1 DR. BONE: Just a second. Dr. Lukert, did
2 you disagree with anything I said?

3 DR. LUKERT: No. As we said, if these had
4 been settled in the clinical trial, you wouldn't
5 have to do this in all these people, but I do think
6 that every single person would have to have vitamin
7 D deficiency ruled out, because these are sick
8 people, and we know that even in well people, the
9 incidence of vitamin D insufficiency is around 10
10 percent, and in sick people, it is somewhere
11 between 20 and 40 percent.

12 DR. POMERANTZ: So, we have these seven
13 and possibly eight things upfront. Then, what do
14 you measure every three to four months now?

15 DR. BONE: I think Dr. Lukert's
16 recommendation, with which I agreed, was we would
17 follow the calcium, the phosphorus, the alkaline
18 phosphatase level, and the 1,25-dihydroxy vitamin D
19 and parathyroid hormone.

20 DR. GULICK: It is worth pointing out we
21 are talking about how you assess these
22 abnormalities on a clinical trial versus what might
23 be done in clinical practice.

24 DR. BONE: I think what the question was,
25 what would we do in clinical practice absent

1 clinical trial data, and that is the answer.

2 DR. GULICK: I think that has led to some
3 confusion, I think among people around the table
4 about what we are recommending to be evaluated,
5 that needs to be done, and then assuming we have
6 that information, what we would actually recommend
7 for safety monitoring in the general clinic.

8 DR. BONE: Well, I think once you know the
9 answer to those questions, and have a mechanism for
10 this problem, you would probably simplify the list,
11 but what the list would be, would be dependent upon
12 what the answers were to those questions for which
13 we don't have the answer now.

14 DR. GULICK: Understood. What you are
15 saying is we need the data before we can really
16 make a clinical care recommendation.

17 DR. BONE: Right, but if you are asking me
18 for a clinical care recommendation without that
19 kind of comprehensive data, I would say you pretty
20 much have to follow those patients on almost the
21 same way that you would if they were in a trial.

22 DR. GULICK: Dr. Goldberger.

23 DR. GOLDBERGER: Given the comments of the
24 last few minutes about bone toxicity, monitoring,
25 et cetera, I was just wondering whether any of the

1 committee members, guests, et cetera, had any other
2 observations to make about what we discussed a few
3 minutes ago, i.e., the broad versus the narrower
4 indications.

5 DR. GULICK: Do you want to change your
6 vote?

7 DR. STANLEY: Yes. It was just occurring
8 to me that we have essentially now restricted its
9 use, because I am not going to use it in a
10 treatment-naive patient if I have got to do all
11 this stuff upfront.

12 DR. JOHNSON: I think if we had done
13 Question 1 last, I am very conservative, and I want
14 to restrict now.

15 DR. GULICK: It's a good thing we didn't
16 take a real vote here.

17 Dr. Tebas.

18 DR. TEBAS: I just wanted to point out
19 that this is advice for the company. I mean we
20 need that in clinical trials. This has been used
21 in more than 500 people for a year, and there were
22 no abnormalities seen in phosphate, phosphaturia in
23 a significant proportion of patients, so I think
24 this needs to be done in the setting of a clinical
25 trial. I mean I don't think we should recommenc

1 these for the whole population before we have that
2 data from the clinical trial.

3 For a year, the abnormalities were not
4 detected in the trials that have been done so far.
5 I think these questions have to be answered in the
6 setting of a clinical trial, and not start doing
7 these parameters in basic clinical HIV practice
8 like mine.

9 DR. GULICK: Again, I think what is going
10 on around the table is that we are revisiting the
11 issue of risk-benefit between naive and experienced
12 patients and where we have the data about these
13 abnormalities, we do have a lot of data in the
14 experienced patients. People are getting a bit
15 more concerned that we simply don't have the data
16 in naive patients, and what would an appropriate
17 way to be to collect the data on a clinical trial
18 setting.

19 Dr. Munk.

20 DR. MUNK: Another question for Dr. Bone
21 as to whether patients with renal insufficiency
22 would warrant special attention.

23 DR. BONE: Well, of course, but I mean you
24 have got a confounder there that most patients with
25 renal insufficiency will have an abnormality of

1 vitamin D metabolism and parathyroid hormone that
2 is similar to what has been described here, but
3 they will have decreased phosphate excretions, so
4 if the problem here is really hypophosphatemia,
5 they will be self-cured.

6 I think that Dr. Lukert's point, the most
7 important single point here probably starting a
8 patient will be to make sure that their baseline
9 vitamin D status is okay, that they are not
10 starting off with a problem related to this.

11 You asked us what the optimal regimen was
12 for monitoring, and we told you what we thought was
13 the optimal way of monitoring. Now, whether you
14 are going to do that in every single patient is a
15 judgment you are going to make.

16 The information we saw from the clinical
17 trial, that was rather limited, but, you know, it
18 wasn't a flashing red light here, but we have got
19 this sort of unresolved question.

20 I suspect that some of this information,
21 some of the concerns we have can be resolved sort
22 of out of inventory, if you will, of information
23 that could be developed from studies that have been
24 completed and are ongoing rather quickly, but make
25 sure you don't have an underlying problem before

1 you start.

2 DR. GULICK: We are going to need to move
3 on. I will take two last comments from Drs. Yogev
4 and Pomerantz.

5 DR. YOGEV: Mine is very quick. Clinical
6 studies, what about pregnant women, is there
7 anything specific that you should test most
8 specifically?

9 DR. BONE: I don't think we can make any
10 specific recommendation about that. What have you
11 got in the way of data in the animals, the fetal
12 toxicity data?

13 DR. YOGEV: I was referring to the women
14 itself.

15 DR. BONE: You are talking about the women
16 or the fetus?

17 DR. YOGEV: The women.

18 DR. BONE: Obviously, it is a challenging
19 environment for both mother and the baby at that
20 point because you have got a lot of mineral
21 mobilization for the fetal skeleton, so they are
22 both at risk if there is a problem.

23 DR. YOGEV: Women are 25 percent of the
24 epidemic, we see more and more kids interested, in
25 preventing the infection, so that is another

1 clinical portion that needs to be added.

2 DR. BONE: I don't know what Dr. Lukert
3 feels, but it is possible we could, with more
4 information from the trials that have been
5 completed than have been exposed to, make a
6 narrower set of recommendations. I don't know
7 that. We are obviously both trying to give you as
8 comprehensive set of tests that you might do,
9 having been asked the question and the way we work.

10 DR. GULICK: We appreciate that.

11 Last comment, Dr. Pomerantz.

12 DR. POMERANTZ: Probably it is my last
13 comment ever at this committee. The comments by
14 Dr. Bone and Dr. Lukert, I think are an important
15 point and show when you don't have data for the
16 virology, you are usually compounded by
17 risk-benefit as you learn a little bit more about
18 the drug, because you didn't vote, you guys, on the
19 original, but yet you added something that I think
20 changed the context of this, I think even with a
21 lot of the people who might have used it upfront
22 before these discussions.

23 I am certainly not going to argue with you
24 on what tests should be obtained, but I do think
25 that it adds yet a third empty data set for using

1 it in naive patients, what happens with high viral
2 loads, what happens in naive patients, and now what
3 happens with the possibility of generating
4 osteomalacia with a panoply of tests that are going
5 to be hard to explain when you have other options
6 for patients who are naive.

7 DR. BONE: That is all taken in the
8 context that osteomalacia is something that is less
9 serious and a lot more easy to fix than HIV. So,
10 you have got to remember what your original purpose
11 was here, of course, as well.

12 DR. GULICK: So, let's summarize this
13 portion just briefly. In terms of impressions
14 about the preclinical data, Dr. Bone really
15 summarized that by saying that there was a signal
16 for safety issues in animal studies.

17 Moving to clinical, again, summarizing
18 saying that based on the data we have, the safety
19 issues do not look severe although there are still
20 quite a few unanswered questions, and as came out
21 in the last couple minutes, particular populations
22 where we simply don't know what the safety issues
23 are, naive patients, renal insufficiency, children,
24 pregnant women.

25 We have limited data based on fracture and

1 densitometry information, but got cautioned about
2 that data, that it really may be preliminary to
3 make conclusions based on the amount we have.

4 In terms of future studies, the strongest
5 recommendation was to identify what the mechanism
6 is here, is it primary renal effect versus direct
7 effect on bone. We got the suggestion from a
8 number of people that long-term and larger
9 follow-up studies are key, and as an example, the
10 903 study which was up there a minute ago, is one
11 such example of that kind of study.

12 We talked about pediatrics, that risks and
13 benefit ratios, particularly in advanced HIV
14 disease, may be tipped one way or the other, that
15 there is certainly a need for drugs and data in
16 this patient population group.

17 A number of studies were suggested that
18 might be looked at, follow-up fracture,
19 densitometry, biopsy studies, cortical bone
20 monitoring, mineral metabolism studies, and then
21 towards the end we began to talk about what might
22 be done to completely characterize this problem,
23 and then jumping from there, what might be
24 recommended in routine clinical practice.

25 As Dr. Pomerantz ended with, in a sense,

1 the committee really began to reassess the risk and
2 benefits given the unknowns about this particular
3 problem.

4 Let's move forward to Question No. 3.
5 Please provide comments on the clinical resistance
6 analyses conducted during the development of
7 tenofovir, provide recommendations for the types of
8 clinical virology analysis that should be conducted
9 for future antiretroviral drug development and
10 suggestions for the type of resistance data and
11 analyses warranting display in package inserts.

12 So, the three issues are let's comment on
13 the resistance data we saw for tenofovir, and then
14 number two would be jumping to the future, what
15 kinds of resistance information would we like to
16 see for new drugs, and then come back to what kind
17 of resistance information should be displayed in
18 the label.

19 Again, we are going to rely on our
20 experts. Dr. Johnson, shall we start with you?

21 DR. JOHNSON: I wrote out some comments,
22 if that is okay. I will be brief. I think Gilead
23 is to be commended again for the extensive
24 phenotypic and genotypic data analyses that were
25 presented, as the FDA, and Gilead beautifully

1 pointed out, all of the data are limited by low
2 numbers, and this is what we face all the time,
3 making definitive statistical conclusions
4 difficult, especially broken out by specific
5 mutations and combinations of mutations as expected
6 in analysis of real world clinical isolates,
7 displaying tremendous heterogeneity.

8 The pooled analyses are what should be
9 evaluated and considered for package insert
10 presentation. We saw more genotypic results and
11 phenotypic results partly in fact because of the
12 low load, but as other patient populations are
13 studied, we should be able to get more information.

14 Jonathan Schapiro pointed out in an
15 excellent fashion that we really would like to see
16 I think a little bit more dissection at a
17 mechanistic level of the patterns of resistance
18 emergence and the stepwise accumulation of
19 mutations, and perhaps there are different
20 pathways.

21 I think Dr. Miller plans on exploring
22 that. That is somewhat analogous to what was done
23 with abacavir. That doesn't impact on package
24 insert labeling, but it is just one of the clinical
25 virology studies that we desperately need to see to

1 understand does this occur in a stepwise fashion,
2 is it an on-off sort of resistance, can you expect
3 ongoing accumulation of other resistance mutations
4 beyond K65R, which leads to the next point.

5 All of the short-term analyses over 24
6 weeks would not in a setting of multi-drug therapy
7 be expected to yield large frequencies of emergence
8 or development of resistance mutations, and we
9 really need longer term data, larger numbers of
10 patients, just as is planned in some of these
11 larger studies, but 24 weeks is not enough to be
12 certain. We heard this glimmer that there were
13 only--I wrote this down--only a few more
14 accumulated, two more week 96 accumulated, a K65R,
15 which to me is one of the ddI-like mutations, and I
16 was rather encouraged by that.

17 We heard in the initial presentations from
18 Gilead that K65R emerged, and we also heard what I
19 think needs to be kind of removed from Gilead's
20 language and labeling languages, unique resistance
21 profile, and Gilead themselves, and I think what
22 everyone would agree that, for example, the K65R
23 mutation is an RT mutation that is associated with
24 resistance to ddC, ddI, and abacavir in vivo, and
25 it is selected by tenofovir in vitro.

1 I just brought along our ISU and say June
2 2000, mutational patterns and showing the overlap
3 with K65R among various drugs in the RT class is
4 another point that I make, that basically I don't
5 know that this is not just another RT inhibitor
6 albeit one that should be in our armamentarium and
7 is active.

8 The reason I say that is whereas
9 previously the in vitro work, the tenofovir was
10 shown to be active against NAMs, the nucleoside
11 resistance mutations like L74V, T69D, two or more
12 of the ZDB associated mutations, and the Q151 and
13 multi-nucleoside complex.

14 We have been shown elegant data by Gilead
15 that there is some potential for cross-resistance
16 in vivo between tenofovir and abacavir, ddI, D4T,
17 ddC, and AZT, and that was shown in the nice way
18 that the FDA pooled the data presented them by the
19 NAMs presentation, where the greater number of NAMs
20 with the 41 and 210 caused some attenuation of the
21 clinical virologic response.

22 Notice that we saw some Virco data for the
23 phenotype still looking like tenofovir was fairly
24 susceptible, which again I found fairly reassuring,
25 but I want to get everybody thinking, as somebody

1 who has gone to every resistance meeting since they
2 started having them, that drugs, even within the RT
3 class, at subtle levels that we don't yet
4 understand mechanistically can contribute to
5 development of resistance and broad intraclass
6 resistance, and perhaps that will happen with
7 tenofovir, not to thwart its approval for salvage,
8 just to make us more vigilant to monitor carefully,
9 to continue to do, and to compliment Gilead again
10 on the extensive, high quality phenotypic and
11 genotypic studies that they have done.

12 I think I will finish with a point that
13 gets to the third thing, is what should go on the
14 package insert. Obviously, discussions about what
15 happens with tenofovir alone with regard to K65R,
16 genotype emergence, because people in the clinic
17 are ordering this drug resistance test they will
18 need to see that and to understand that the
19 increase with regard to the 4-fold and tenofovir
20 susceptibility knocks out response. That needs to
21 be in there just for tenofovir alone.

22 With regard to cross-resistance, we would
23 like to see perhaps a table that did get to, if you
24 have got three or four NAMS with 210 and 41, X
25 percent of the patients might have an expected

1 virologic response. I think that will be very
2 helpful. I realize that is unprecedented for the
3 FDA.

4 I looked back and brought the abacavir
5 package insert even though they have got similar
6 diminution of response even particularly in the
7 setting of 3TC and AZT with backbone nucleoside
8 mutations that we are in a different era, it is
9 2001, people are ordering resistance tests, and the
10 question they are going to ask in salvage is to
11 save money, cost, toxicity, whatever, will this
12 drug have a chance of working in my patient. That
13 is just another thing to consider.

14 I think I will stop there except to again
15 maybe bring us back to something I raised earlier
16 this morning, and something that I believe one of
17 the community people raised is what is the role of
18 3TC and the M184V, and my read of this again was
19 that that enhanced activity was lost when 70
20 percent of the subjects had a NAMS present, making
21 if it could possibly be on the label, I think the
22 clinicians want to know do I need to continue 3TC
23 or not, some presentation of that data, letting the
24 people decide whether they think that it will work
25 or not, to leave it in the regimen would be

1 helpful. I will stop there.

2 DR. GULICK: Thank you.

3 Dr. Struble and then Dr. Schapiro.

4 DR. STRUBLE: So, Dr. Johnson, I guess you
5 are in favor of putting as much resistance
6 information in the labeling as possible even though
7 that some of these mutations may be based on a
8 small subset of patients and putting the
9 appropriate caveats, is that what you would like to
10 see?

11 DR. JOHNSON: Yes.

12 DR. GULICK: Dr. Schapiro.

13 DR. SCHAPIRO: I would agree with Dr.
14 Johnson's comments. I would also start by saying
15 that I also think that we had some very nice
16 virology data. I think the folks from Gilead
17 should definitely be congratulated. These are both
18 expensive and smart studies, and I think that
19 definitely we have seen much more than with
20 previous drugs, and I think that is very important.

21 I think also the folks from the FDA, both
22 have the last couple of years made a big effort to
23 bring resistance to the forefront. I think this
24 drug and the previous drug that was discussed both
25 have much more than in the past, and I think it

1 shows some cause and effect, that by bringing this
2 and discussing it, we are getting better resistance
3 data.

4 As Dr. Johnson said, not long ago we
5 weren't seeing almost any of this. I also think
6 the analysis that was done was very helpful that
7 Kim presented.

8 I will answer the three things together.
9 I think that the resistance, it is important that
10 we not take a step backwards. We know resistance
11 is not a dichotomy, it is not yes or no. There is
12 a reduction in sensitivity that we see which
13 requires additional drug. That is how we look at
14 resistance, and it is very, very important not to
15 go back to saying yes or no resistance. There is
16 no such thing.

17 There are reductions in sensitivity, and
18 we saw data presented in that way, and we should
19 not find ourselves lumping data to get statistics,
20 and then lose this effect. I think that the minute
21 the study, the large study that most of the data is
22 coming from does not allow patients with high viral
23 loads. We are not going to get enough data. Those
24 are the patients with the mutations.

25 The minute I think any of us saw that the

1 patients had 400 CD4 and 5,000 viral load, we knew
2 we were not going to get enough to get correlates,
3 and I think it was understandable that to enroll
4 those patients we needed that, but I was not
5 surprised that we don't see mutations.

6 We know, Vicki and I look at resistance
7 assays. There are a lot of patients with five or
8 six NAMs or TAMs, and there are almost none in this
9 study. We see those every day. So, when you limit
10 it, we didn't have any chance of getting enough
11 mutations because of all these different
12 combinations.

13 So, I think that in the future, it would
14 be very important to somehow, yes, enroll patients
15 with mutations in order for us to have enough. I
16 also think that what is missing is the correlates
17 between specific genotypic patterns and the
18 phenotypic change.

19 Articles have been published. There are
20 panels now of isolates, both clinical and
21 laboratory, which are tested in a standard way, and
22 that gives us a lot of insight. So, I think that
23 is missing from the data set.

24 I think that in future studies, we have to
25 delineate the issue of 184. It is surprising that

1 some very convincing in vitro data was not
2 supported. The data here does not support that
3 clinically it panned out, and that is curious. It
4 is also key because the clinical question which
5 came up a number of times this morning, do I
6 continue 3TC or not, will come up and that is very
7 important, and it may come up for abacavir and
8 other drugs, as well. So, that should be looked
9 at.

10 Regarding the label, I think it is key to
11 show as much information as possible, and I think
12 in this case, even though we do not have
13 statistical significance, we want to show the
14 tables. I think Table IVE, that Kim showed, and
15 actually IVD, those are the two summary tables are
16 very important and they are key, and whether we got
17 statistical significance or not is unfortunate, but
18 I think often we don't.

19 I think we have to remember that both
20 genotypic and phenotypic assays are now being used
21 routinely. In order to interpret these, we need
22 exactly the data that Gilead provided us. We
23 actually have these mutations or this phenotypic
24 change provided this much of viral load reduction.

25 That is the data that we are now

1 scrambling for anxiously with our previous drugs,
2 and we have the benefit of the good work done by
3 Gilead, and we definitely, definitely should
4 include that, and I would not lump that together to
5 get a p value. I think that would be a mistake,
6 and I think the key would be a phenotypic assay
7 that shows a 3.5 reduction. If you lump and use 4,
8 that will read out as sensitive.

9 If you provide this data in the label, you
10 can look and see that although there is still
11 activity, it is less than you see if it's 1 or 1
12 1/2, and I would be very, very cautious not to run
13 back to statistics and lump that together.

14 I think an example again, if we show slide
15 No. 6 that was shown in the beginning, which uses
16 the conventional cutoffs, and we have 3-fold and
17 10-fold, is totally irrelevant to what was shown
18 afterwards.

19 So, I would show those nice tables even
20 though they don't have statistical significance.
21 Maybe we will have studies in the future which
22 will, but I would not back off and lump them again
23 together to get p values.

24 DR. GULICK: Other comments from the
25 committee?

1 Dr. DeGruttola.

2 DR. DeGRUTTOLA: I also thought it was
3 great to see all the resistance information, and I
4 like the way the Gilead presentation made
5 distinction between the protocol- specified
6 analyses and exploratory analyses that were done
7 later.

8 I also like the presentation that Dr.
9 Struble made. I like the fact that all of the TAMs
10 were listed, so that you could look at each of them
11 individually and then look at different
12 combinations as we have discussed.

13 I think one additional thing that might be
14 interesting is to look at the proportion of the
15 variability in response, the DAVG, that is
16 explained by the mutation patterns, and there are a
17 number of different ways of doing that. That
18 obviously gives you some sense of how important the
19 sequences are in capturing variability and how much
20 variability is left over to be explained by other
21 things including perhaps other mutations that
22 haven't been looked at, as well as, of course,
23 other factors. So, I think that might potentially
24 be of interest.

25 The other thing is the issue, Dr. Struble

1 mentioned this morning the question of what do you
2 do about the fact that if you do formal statistical
3 testing, you are doing many tests, so how do you
4 adjust for the multiple testing, and I think that
5 that is an open area of research. I don't think
6 that has been resolved in resistance analyses. Of
7 course, there are common statistical procedures for
8 adjustment that are probably too conservative in
9 this case.

10 This is an informal recommendation, but
11 just a suggestion that perhaps people might want to
12 look at other kinds of exploratory techniques like
13 clustering and partitioning, obviously only for the
14 exploratory analyses.

15 DR. GULICK: Dr. Johnson.

16 DR. JOHNSON: I just wanted to make one
17 other comment I overlooked in what you would say
18 about tenofovir directly.

19 If you look at Table 4.14 in the Gilead
20 tables, as well as the FDA Table 4A, you will see
21 that the L74B VRI substitutions, although the
22 numbers were very small, at tenofovir 300 mg, there
23 was really no viral load reduction, and I think you
24 could maybe think about mechanisms, ddI is also
25 DATP-like, mirroring the natural substrate for RT,

1 which maybe for ddI, has been one of the reasons it
2 is hard to develop resistance, as Doug Richmond has
3 taught us. Maybe the same is true for tenofovir to
4 explain this development, but we may want to put a
5 cautionary note that having not just the K65R, but
6 L74V or I, were likely to abrogate response, as
7 well as ditto the T69S insertions, the Q151M, which
8 we knew about from in vitro work.

9 DR. GULICK: Dr. Hamilton.

10 DR. HAMILTON: I don't think it would do
11 just to hear from the true believers here. As
12 inexpert as some of us may be, there is a large
13 group out there who are not convinced that using
14 genotypic, phenotypic analyses in fact do have,
15 have been proven to have an effect on the clinical
16 outcome of patients with HIV infection.

17 To my knowledge, this knowledge, as
18 important as it is virologically and biologically,
19 and it is interesting and fascinating and detailed
20 as it is, has not been used to my knowledge to
21 prevent the emergence of these resistance patterns.

22 Does this mean that we shouldn't provide
23 this information to the users, the consumers of
24 this product? No, it doesn't mean that, but it is
25 going to change. I haven't seen an anti-infective

1 agent yet whose resistance pattern doesn't change
2 after it is in use.

3 So, if you are going to put it in the
4 package insert, you ought to plan on changing it
5 every so often, because it certainly is going to
6 change. So, I am not so much arguing with the
7 comments made by others here, but just interjecting
8 the more general comment that I am not certain we
9 are overdoing this issue.

10 DR. GULICK: Dr. Schapiro.

11 DR. SCHAPIRO: First of all, I think there
12 is virologic data that these help. I don't know if
13 we have data that this prevents additional
14 mutations. I think we have indirect evidence
15 because we know that reducing the viral load does
16 reduce the generation of mutations, but I agree
17 that we don't have outcome data for the patients.
18 That might require longer follow up.

19 I do think also that, as you said,
20 resistance patterns will change. I think we
21 definitely are looking only at one type of
22 resistance. I think it is evident. Dr. Johnson
23 mentioned ddI, and I think that for protease
24 inhibitors, as well, there are other mechanisms of
25 resistance. Some of them may be cellular, and we

1 are simply looking at one of them.

2 I think Dr. DeGruttola, one of his
3 comments was we could quantify how much this
4 resistance is really responsible for those changes
5 in the viral load, and that might be important.

6 I think that by providing the data in the
7 package inserts, we allow people who do want to use
8 this to see the data. I don't think we necessarily
9 have to, that forces them to use it, but I think it
10 is a pity where we have this high quality data,
11 which we don't have with the others, not to include
12 it, and I agree definitely that we are probably in
13 for some surprises.

14 DR. GULICK: Other comments from the
15 committee? Yes, Dr. Englund.

16 DR. ENGLUND: I just wanted to say that
17 for some of the resistance data, it changes so fast
18 and those people who clinically use it, can access
19 the Internet and have other access to things, that
20 one of the things I would recommend is putting in
21 the package insert something like Table 4D, which
22 is a nice, general table. This goes any TAMs
23 instead of giving so much specific things which are
24 going to change in two months when they more
25 studies done.

1 DR. SCHAPIRO: Just to mention that the
2 publication that Dr. Johnson showed is actually on
3 the Internet and is updated.

4 DR. ENGLUND: My patients bring it in,
5 too. Maybe sometimes they know more than some of
6 us. But I like the idea of for package inserts, to
7 not know that you are going to be outdated before
8 it comes out, I would be a little concerned about
9 that. It is great data.

10 I like the idea of having a table. I like
11 it in the package insert, but to perhaps include
12 things that are a little more generalizable, like
13 this 4D, which shows any TAMs instead of every
14 specific mutation, because absolutely that is going
15 to change, and it is going to change by the next
16 AIDS meeting.

17 DR. GULICK: Dr. Sun.

18 DR. SUN: I would just like to make the
19 point that I think for this kind of data, the
20 standard should be different than that for clinical
21 trials. I think by the nature of this kind of
22 work, it is generally retrospective, it is
23 exploratory, which doesn't mean it is not robust.
24 I think you can apply robustness by doing your
25 statistics in a robust way and doing sensitivity

1 analyses, but I do think it is useful to have this
2 kind of information label, if for no other reason
3 than to try to get some standardization of
4 interpretation for individual drugs.

5 I would recommend to the sponsor that
6 whatever is in the label, you try to also have the
7 resistance testing companies adhere to that, so
8 that not every resistance test that is available in
9 the marketplace, some of which are not regulated,
10 has their own set of rules and leaves physicians
11 extremely confused.

12 DR. GULICK: I will just try to summarize
13 this part. In terms of the assessment of the
14 resistance data presented by Gilead, the committee
15 really would like to commend Gilead on providing
16 extensive, high-quality data that people found
17 quite useful.

18 Having said that, people raised concerns
19 about low numbers of patients, the heterogeneity of
20 the resistance patterns we saw, and perhaps that
21 the patient population studied was not particularly
22 ideal in that they had relatively limited viral
23 load levels and high CD4 cell counts.

24 The information we saw was genotypic much
25 more than phenotypic, and the potential for

1 cross-resistance among the available drugs was
2 addressed.

3 In terms of the future analyses, we mostly
4 centered on what more we would like to see
5 concerning tenofovir, although many of these areas
6 could be extrapolated to future compounds also.

7 Dr. Johnson suggested that perhaps the
8 most valuable information would be to really
9 carefully characterize the pathway, the patterns of
10 the development of resistance over time, what are
11 the ongoing steps in changes that confer
12 resistance.

13 We agreed that longer term data would be
14 very helpful, noting that what we saw was really 24
15 weeks of data. We would like to see longer term
16 data in larger numbers of patients. Again, going
17 back to the patient population, it will be very
18 interesting to see what kinds of patterns emerge in
19 a highly treatment-experienced population with high
20 viral load levels.

21 Dr. Schapiro called for analyses which
22 correlate the genotypic and phenotypic approaches.
23 Several people mentioned that we would like to
24 clarify the M184V data, particularly for clinicians
25 who were struggling with whether to continue 3TC or

1 not.

2 Dr. DeGruttola made some suggestions about
3 analyses that could be done, looking at variability
4 of mutations and how to address the problem of
5 multiple comparisons including novel techniques
6 like clustering and partition analysis.

7 In terms of the label itself, people felt
8 generally that resistance data was extremely
9 helpful, that this was bringing us into 2001, that
10 we really do need to update the label as the field
11 matures with regard to providing the data that is
12 available to clinicians.

13 There were several words of caution, one
14 being that perhaps the resistance data we have will
15 change so quickly that the label could rapidly
16 become outdated. Also, the caution that most of
17 the data we are seeing is exploratory and
18 retrospective, but the general feeling, I think
19 among the committee, was that yes, we would like to
20 see this information.

21 In terms of how to portray it, people felt
22 that they liked the table format specifically from
23 the FDA analysis 4D, which was a summary table of
24 the genotypic patterns, and 4E, which was the
25 summary data for the phenotypic patterns.

1 There was a call for defining cutoffs if
2 they are known, particularly for phenotype, and a
3 general call for providing pooled data, but with
4 inherent problems about small cell numbers in terms
5 of doing statistics, but an urge to provide data in
6 a way that was interpretable to clinicians, and
7 that is going to be an ongoing battle I think to do
8 that.

9 There was a caution about claiming that a
10 drug has a unique resistance profile and that the
11 potential for cross-resistance, among other drugs
12 that are currently available, be outlined in the
13 label if there is data to address that issue.

14 Finally, Dr. Sun led the charge that we
15 really need a standardization of resistance
16 information particularly if it is going to enter
17 into labels for newer antiretroviral therapy.

18 Dr. DeGruttola.

19 DR. DeGRUTTOLA: I wanted to make one
20 comment that may not have been clear. Dr. Gulick
21 mentioned looking at the variability of sequences,
22 which I think may be an interesting thing to do,
23 but what I had intended to apply was to look at the
24 variability in response of the patients, in other
25 words, the DAVG or whatever the response measure

1 is, and see how much of that variability is
2 explained or capture by the resistance information.

3 DR. GULICK: Thanks for the correction.

4 From the Agency point of view, were there
5 other things with this particular question that you
6 wanted us to address?

7 DR. STRUBLE: No, I think we got the
8 feedback that we were looking for. Thank you.

9 DR. GULICK: Got it, huh?

10 DR. STRUBLE: Yup.

11 DR. GULICK: Let's move to the last
12 question.

13 Please provide comments on the applicant's
14 proposed second study for traditional approval, and
15 provide comments for other study designs or patient
16 populations that should be studied as part of Phase
17 4 commitments.

18 Let's again break this into two sections.
19 Let's take a look at the proposed pediatric study.

20 [Slide.]

21 Let's first consider this study design,
22 which they are proposing in pediatrics.

23 Dr. Yogev.

24 DR. YOGEV: I think the most important
25 part is I don't see on what is here, wasn't

1 mentioned stratification of the population. I
2 think it is completely different than the
3 pediatric. The pediatric in the older group are
4 very different than two years of age and younger.

5 We recently are finding out even if you go
6 less than two years of age, there are differences
7 in between the one month to the three months and
8 six months. I mentioned before, I just want to
9 stress I don't understand why less than six months
10 are not included.

11 Maybe there is some logic in the two
12 weeks, then stop, reassess, and do another one as
13 in intensification versus how tenofovir in the new
14 setup is working. I am not sure that that will
15 give you the answers.

16 Obviously, the PK was not mentioned, I am
17 not sure what they are looking for. I think this
18 is one of the issues. We, in the past, I just hope
19 we will not repeat the same mistakes which we did
20 with the AZT. A lot of us still remember, many of
21 us, that we woke the patient every two hours and
22 then four hours and then six hours.

23 This drug is intracellular, and there are
24 some data to suggest that maybe in pediatric, for
25 some reason, mononuclear cells are more affected, a

1 higher percentage of them are affected in the
2 process than the lymphocytes, and when you look
3 into the PBS results in vitro versus lymphocytes,
4 it is interesting that is much more sensitive, that
5 maybe you don't need that much.

6 So, maybe where we need to look is really
7 to avoid toxicity of the bone, whatever, is
8 intracellular levels in activity, which I don't see
9 in what is recommended here.

10 DR. GULICK: As I recall, the sponsor has
11 planned PK studies apart from this in pediatrics,
12 is that not true?

13 DR. YOGEV: But it is an escalating dose
14 which I presume if they go by the classical one,
15 they try to compare it to what will happen in
16 adult, and I am not sure that's in pediatric the
17 right way to do it. I don't see it in this one.

18 DR. GULICK: Let me take a step back and
19 just remind people why we are looking at this study
20 design. So, this would be the second study to
21 receive full approval, and this would be going with
22 the 903 study, which is the study we have been
23 talking about most of the day in naive patients.

24 So, this is a two-part hybrid, and I think
25 we coined that term at this table with some help

1 from some others. So, it is looking at a
2 population of children, viral load levels greater
3 than 30,000, reduced CD4 percent as outlined there,
4 and treatment-experienced defined as having one
5 member of each drug class.

6 They are on stable antiretroviral therapy
7 and then are randomized 1 to 1 to either add
8 tenofovir or placebo for two weeks. That is
9 looking at the virologic activity, and then
10 optimizing the baseline based on genotypic tests,
11 which were--or genotypic and phenotypic--genotypic
12 tests which were performed at baseline to optimize
13 the background drugs, and then both are continued
14 for 46 weeks.

15 So, two different endpoints, two different
16 parts to the study. That is what makes it a
17 two-part hybrid. Okay.

18 So, other comments on this design? Dr.
19 Schapiro.

20 DR. SCHAPIRO: As you mentioned, this was
21 discussed at a previous meeting. I think it is
22 important to realize that the first two weeks are
23 very precious, and it is probably important to get
24 more than one viral load measurement, and that is
25 key. I think it is important that a byproduct of

1 this is we can get very tight correlations between
2 baseline resistance patterns and two-week viral
3 load outcomes, which I think will enhance a lot of
4 the understanding of resistance.

5 So, I think this will give us good
6 efficacy data, but I think it will also contribute
7 a lot to some of the questions that Dr. Johnson and
8 I and Dr. DeGruttola were bringing up, so I think
9 that could be of good value, but it is important
10 not to lose the benefit of the first two weeks even
11 at the expense of having the kid give blood another
12 couple of times during that period for additional
13 time points.

14 DR. STRUBLE: Dr. Schapiro, how often do
15 you think that viral load should be measured in the
16 first two weeks?

17 DR. SCHAPIRO: First of all, I would make
18 sure you have a good baseline, and what we don't
19 want to have is zero in two weeks. I mean we can
20 wait a second for Victor to give his opinion, as
21 well, but I think that the caution here is an end
22 to have a pretty good definition of where the
23 patient started and where they went in two weeks.

24 In addition, there have been some studies
25 that I think Victor may have been part of it, where

1 the slope actually can be looked at, which you
2 would need additional time points. I would at the
3 very least take it one week and at two weeks, and I
4 would be interested to what Victor thinks would be
5 valuable as far as how many time points of viral
6 load in the first two weeks are necessary.

7 DR. DeGRUTTOLA: It obviously had to do
8 with the degree of accuracy that you want to be
9 able to estimate that slope, and the amount of
10 power that you require in order to make the
11 comparisons.

12 Those kinds of calculations have been
13 done, so that it is possible to see how much
14 additional power you gain by adding additional time
15 points. I don't have specific recommendations
16 right now.

17 The other issue, of course, is if you are
18 interested in getting any of the fine detail of the
19 response over the first two weeks, but usually that
20 is less of an issue than just being able to make
21 the comparison itself.

22 DR. GULICK: Dr. Wong and then Dr.
23 Englund.

24 DR. WONG: I have a little bit of a
25 different comment about this. I expect that the

1 results of this are to a great measure going to be
2 determined, or at least in part, by how good the
3 optimized background regimens are and perhaps also
4 how different they are from what the patients have
5 been receiving before.

6 I am a little worried that superiority of
7 adding tenofovir might not be able to be shown
8 depending on how good the change is from the
9 background regimen to the new regimen.

10 If the null hypothesis here, well, if the
11 hypothesis that is being tested here is that
12 tenofovir, when added to another regimen, gives a
13 durable result, I think that one of the things we
14 saw here today from Study 902 is that the answer to
15 that is yes, it does.

16 So, I am not sure that I would conclude,
17 even if this study turned out to be negative, if
18 the new study on the naive patients gives a
19 clear-cut result for 48 weeks, and the results in
20 902 really pass FDA review when all of the data can
21 be scrutinized, that I might not conclude that the
22 hypothesis has been shown whether or not this
23 happens.

24 Now, that is not to say that I don't think
25 this study should be done, because we clearly need

1 to do studies such as this in children, but it is
2 possible that this will give a negative result even
3 if the drug is effective and durable, and that
4 might be able to be shown before this is completed
5 or even started.

6 DR. GULICK: Could we ask the sponsor, the
7 sample size and what power of a difference in
8 virologic response that the study is looking for?
9 I am sorry, it says n equals 100. What kind of
10 difference are you powered to detect?

11 DR. TOOLE: DAVG, 0.5 difference between
12 tenofovir and placebo.

13 DR. GULICK: 0.5 logs?

14 DR. TOOLE: 0.5 logs.

15 DR. GULICK: Over 48 weeks.

16 DR. TOOLE: Over 40 weeks. We are also
17 considering either changing the DAVG40 as the
18 second endpoint to time to failure, as well.

19 DR. WONG: I guess maybe my real question
20 is to the Agency, how do they interpret the results
21 in the sponsor's Slide 22 with respect to
22 durability of antiviral effect of tenofovir?

23 DR. STRUBLE: I think we overall
24 fundamentally agree with the results, but however,
25 after week 24, there are a lot of treatments

1 switches that happened on the tenofovir arms.

2 So, although it appears that it is a
3 durable response, we have to take a closer look to
4 make sure that response wasn't attributed to the
5 addition of new drugs over the last 24 weeks.

6 DR. WONG: If you were to decide that that
7 was not the explanation and the naive study that is
8 currently underway should show an effect, then, it
9 would seem to me that the major burdens are met,
10 right, no matter what this study shows.

11 DR. STRUBLE: I think we looked at all the
12 data in the entirety with the evidence from the
13 902, the results of this study, the naive study.
14 We look at the data as a whole to make the
15 determination for traditional approval, and I think
16 all that information will help.

17 DR. GULICK: Dr. Englund.

18 DR. ENGLUND: Just a couple comments about
19 the pediatric study. First of all, I am wondering
20 why there is a two-week--and I wasn't involved in
21 this--why there is just a two-week addition of the
22 single drug, because one of the concerns I have is
23 if you do optimize everyone's regimen as was said,
24 you may optimize everyone's regimen with or without
25 the tenofovir.

1 If you expanded the first initial two-week
2 introductory period, you went to, I don't know,
3 four weeks or eight weeks, you would actually mimic
4 what you have done in the adult trial, and you
5 would at least get some baseline data to show that,
6 as a single agent, that it works, and you could get
7 more virology data, you could get more points in
8 time to actually look at the resistance, and that
9 is one suggestion.

10 The second one is agreeing with Dr. Yogev.
11 I think it needs to be stratified at the very least
12 into younger children and older children because
13 there is a big difference between two-year-olds and
14 12-year-olds, but I mean two to six, maybe we could
15 put together, but certainly you get over the age of
16 six, and there is a lot of difference in just PK
17 studies and disposition of drug.

18 DR. GULICK: Just by way of background,
19 the committee actually spent a whole session on the
20 design of salvage therapy studies. We had a lot of
21 debate about the point that you raised, how much of
22 an initial period do you want one drug versus
23 placebo to try to assess antiretroviral activity.

24 There were a number of opinions about
25 that. Two weeks was one option in terms of

1 bouncing risks and benefits. It may not be the
2 only way to do it certainly.

3 Dr. Sun.

4 DR. SUN: Just an observation and a
5 question. Why should this study be restricted to
6 people that have failed all three classes of drugs?
7 If you look at the overall clinical data that you
8 have at the end of the day, 902 and 907 are in
9 heavily experienced patients. 903 is going to be
10 in naive patients, and there is plenty of patients
11 who are experienced with one or two classes. It
12 seems like that might be an opportunity to do a
13 clinical trial.

14 DR. STRUBLE: So, you are saying in
15 patients that only have experience with one or two
16 classes?

17 DR. SUN: One or two classes.

18 DR. STRUBLE: As a possibility?

19 DR. SUN: Right. Just to have a broader
20 patient population exposed to the drug.

21 DR. GULICK: You said two different
22 things, and we should be clear about it. You said
23 experienced with all three classes, and then you
24 said failed all three classes. Clearly, there is a
25 difference between those.

1 This says experienced as currently
2 written, so your point applies, but just to make
3 that distinction for the committee.

4 Dr. Schapiro.

5 DR. SCHAPIRO: Just to address both the
6 comments of Dr. Wong and Dr. Sun. There is a
7 tradeoff here. We assume that the optimizing will
8 not bring the patients undetectable, and therefore
9 it does matter a little bit.

10 I think we have to design this feeling
11 that there will be a delta between adding our new
12 drug on the optimized background versus the
13 optimized background, so we do have to have a sick
14 enough patient population that there will not be,
15 in the majority of them, undetectable viral load
16 with optimization.

17 That is why this was part of that very
18 elaborate discussion we had. The tradeoff with the
19 two, four, and eight weeks that were discussed is,
20 on the one hand, as you said, the longer we go, the
21 more data we have, but, of course, we don't want
22 patients who develop mutations by having effective
23 monotherapy in a way.

24 Here, for example, we believe that if you
25 optimize background, you might prevent, let's say,

1 the K65R, the longer we go without that, we would
2 have a greater--so, these are the tradeoffs, and we
3 did have a whole session on it, but I think these
4 were some of the things that we had discussed, and
5 I think that is sort of how we came to two weeks as
6 one option.

7 DR. GULICK: Dr. Stanley.

8 DR. STANLEY: But again, in this
9 particular case, we now have data from the 902 and
10 907, where adding it on, they didn't high level of
11 resistance. There was the 3 percent that developed,
12 but I am just saying with this particular--that was
13 a concern why we settled on two weeks previously,
14 because we were afraid of adding a drug and getting
15 rapid development of resistance.

16 There is at least some data here that
17 would suggest that that is not a tremendous
18 upswing, but does that apply to children, I don't
19 know.

20 DR. GULICK: Does that apply to all levels
21 of viral load?

22 DR. STANLEY: Right, and to the 30,000
23 viral load.

24 DR. SCHAPIRO: Here, you are generating
25 more, I mean we have 30,000, so I think there is a

1 danger of that.

2 DR. GULICK: Dr. Yogev.

3 DR. YOGEV: Just for the sake of the kids,
4 I don't think we should ask the company to take
5 more blood, viral load, in the first two weeks. It
6 is a very interesting issue, but multiple studies
7 show that you get to a certain point, and that's
8 it.

9 This is a clinical study, so if you want
10 to do a subgroup I won't argue. As for the old
11 classes, many of our patients will be on two
12 classes that will open it really to enroll many
13 more patients because our next step will be for
14 three, so those will be more expense than
15 experience can be, and that becomes a salvage
16 protocol, and it would be interesting for the
17 experience to be in it.

18 So, I would suggest go to two classes, and
19 as for the n, the combination, correct me, but I
20 thought they mentioned 100 patients. I don't think
21 with this type of study, 100 would be sufficient,
22 and they need to work it out to get the right
23 number.

24 Why are we stopping in 48 weeks if it is
25 working? Why shouldn't the study go to 96 and

1 above? One of the major problems is when you stop
2 what you are doing, so I think as long as we see
3 that there are data, and we have a question on
4 toxicity, whatever longer, especially this
5 population, I highly recommend to go to longer
6 period of the study, not necessarily to get
7 approval from the FDA.

8 DR. GULICK: Can we ask the sponsor just
9 in follow up to that, would there be plans to
10 extend or have a rollover study for the children in
11 this study?

12 DR. TOOLE: [Off mike.]

13 DR. GULICK: So, the answer was that they
14 would have continued access to tenofovir.

15 DR. YOGEV: I was not afraid of access
16 because immediate they proved it out, we have an
17 access. We were surprised to find out the drug
18 like ritonavir, the toxicity in several of our
19 patients appeared very foreign to the study, which
20 were not known to the adult, and I am just trying
21 to raise the issue of safety.

22 DR. GULICK: So, you are visiting an issue
23 that we visited earlier today, which is to say we
24 need longer term safety, not just in adults, but
25 pediatrics, too.

1 Dr. Struble.

2 DR. STRUBLE: I would just like to bring
3 up with the treatment experience, I think one of
4 the reasons why it is treatment-experienced with
5 all three drug classes is because of the bone
6 toxicity issue in children, is that I think that
7 the risk may be different in children, and I think
8 that we are choosing a patient population that will
9 accept a little more risk versus choosing a patient
10 population that may be experienced with one or two
11 drug classes.

12 I think what they propose is a reasonable
13 approach at this time until we fully understand the
14 true mechanism and have some additional long-term
15 safety.

16 DR. YOGEV: If you do that, just be
17 prepared, you are going to have very few kids less
18 than two years of age who are going to be on three
19 classes.

20 DR. STRUBLE: We realize that.

21 DR. YOGEV: Unfortunately, you get what
22 happened was more than we would like to see in
23 pediatrics. The drug was approved for much lower
24 age group.

25 DR. STRUBLE: We are going to be getting

1 that from pharmacokinetic studies, stratifying by
2 age. We will get some pharmacokinetics in younger
3 children that might not necessarily fit into this,
4 and some long-term safety.

5 DR. YOGEV: But those are short studies.
6 As long as they go long in high number, because I
7 think the bone is very rare, and you might find it,
8 but--

9 DR. STRUBLE: One of the PK studies is a
10 48-week study.

11 DR. GULICK: Let's come to some
12 conclusions about this. The consensus of the
13 committee is that we like this design, it was one
14 of the ones that we actually came up with at our
15 salvage session last year, so we are supportive.

16 We talked about the tradeoffs of doing two
17 weeks in terms of ability to detect a difference
18 depending on viral load level, the risk of
19 mutations, the risk or prior experience, some
20 debate about whether two versus three drugs is
21 appropriate, and then assessing risk versus benefit
22 in those patients particularly with toxicity in
23 mind.

24 Dr. Wong raised the point what if no
25 difference is detected here, and the answer from

1 the Agency's point of view was really we need to
2 consider this in the context of all the studies.

3 There were some concerns about
4 stratification based on ages from a couple of our
5 pediatricians, also PK and safety issues, and
6 finally, that the first two weeks is the critical
7 part of this study, so that the number of samples
8 should be appropriate to really detect a
9 difference.

10 In the last remaining minutes, let's
11 consider as a group other studies that we would
12 like to see, and particularly the Phase IV
13 commitments that we would suggest to tackle some of
14 the issue we have been considering all day.

15 Dr. Munk jumping in.

16 DR. MUNK: Jumping in. With the Chair's
17 indulgence, slightly off topic.

18 DR. GULICK: Ooh.

19 DR. MUNK: This is a request to the
20 sponsor, as well as to the Agency. I am assuming
21 that tenofovir will be indicated to be taken with
22 food, and my request is that in all the
23 documentation that we have received, there are
24 references to a high fat meal, a standardized high
25 fat meal, and the request is that in any case where

1 there is a food indication or requirement, that the
2 terms meal, high fat meal, snack be translated in
3 patient-oriented materials into very concrete lists
4 of food.

5 Does a high fat meal mean a Big Mac and
6 fries, or a cheeseburger with a milkshake? And
7 that is really literally the level of detail that I
8 think is needed in food lists. I can't tell you
9 how many inquiries I have gotten about what does a
10 snack mean, what does a light meal mean, and so
11 just providing kilocalories and percent calories
12 from fat is not enough.

13 DR. STRUBLE: We hear this comment quite
14 often from patients actually receiving the
15 products. You know, a high fat meal, our Clin
16 Pharm people can comment actually more, but there
17 is a standardized meal that they take to do these
18 studies, but the clinical trials were done,
19 patients were instructed to take tenofovir with a
20 meal, and that is what the proposed wording is.
21 There was no set meal that people had to take.

22 DR. MUNK: I guess, then, just a footnote
23 would be if that is the case, then, that needs to
24 be communicated to patients that the patients were
25 simply instructed to take it with a meal, and that

1 that is what all these clinical results were based
2 on.

3 DR. STRUBLE: That is a very good point,
4 thank you.

5 DR. GULICK: Let's shift gears back to
6 Phase IV commitments. Dr. Schapiro.

7 DR. SCHAPIRO: Dr. Fletcher isn't here
8 with us today, so I think drug interactions are
9 underrepresented, but I do think that if he were
10 here, we would be hearing that we definitely have
11 to do the studies and that you can predict them.

12 I think that the possible interaction with
13 Kaletra would not be expected with what we know
14 from people. I think we do have to do those
15 studies. I think that is actually something which
16 we really, really need to have interactions. They
17 don't take long, but I think those need to be done.

18 I also think honestly, we saw very little
19 data actually looking at the appropriate dose. I
20 think the 600 dose was started with actually four
21 experienced patients, a total of versus eight
22 patients. There was very little data.

23 I would be cautious to just go forward.
24 We have seen with other drugs that the community
25 may react in a way that they have done with other

1 drugs, that if there is not a good answer, then, we
2 get a lot of experimentation being done, and if
3 this drug may have toxicity that is dose related,
4 it might be better that that be done in an
5 organized way, and not that we find ourselves like
6 the PIs now, having everyone use a different one,
7 so those would be two that I would suggest.

8 DR. GULICK: Do you want us to get more
9 specific about drug interactions?

10 DR. STRUBLE: I was just going to ask Dr.
11 Schapiro that question. What specific drug
12 interactions would you like to see?

13 DR. SCHAPIRO: The first one that comes to
14 mind, which I was concerned about, was the
15 ritonavir.

16 DR. STRUBLE: With different doses of
17 ritonavir?

18 DR. SCHAPIRO: Well, Kaletra is 133 mg of
19 ritonavir, and that actually had a significant
20 increase in tenofovir. If that is linear, then, a
21 dose which is very commonly used in the patients
22 who will be receiving that drug, the minute we
23 approve it, will be patients who get 400, which
24 could give a much higher interaction, and some of
25 the toxicities, which we are worried about, we have

1 no data on what happens if you have twice the
2 levels.

3 The first one I would jump into, I think
4 also, I don't know for the NRTIs what was done, if
5 they were covered, but I think the first one I
6 would do right away would be 400 mg of ritonavir to
7 start with, and I would probably look at the other
8 NRTIs, as well.

9 DR. STRUBLE: Sustiva was done, 3TC was
10 done, ddI with the old formulation was done. They
11 are going to go back and do the enteric coated,
12 because there was an interaction with ddI with the
13 buffered formula.

14 DR. SCHAPIRO: And nevirapine?

15 DR. STRUBLE: Sustiva was done.
16 Nevirapine, I don't believe was done, no.

17 DR. GULICK: So, would you suggest
18 nevirapine?

19 DR. SCHAPIRO: I am a little bit lost, but
20 I think that is an important thing to be done,
21 because we are going to be combining that as soon
22 as it comes out.

23 DR. GULICK: Dr. Yogev.

24 DR. YOGEV: I think you mentioned before
25 saquinavir as an issue that was not resolved, which

1 I think should go, and to my surprise, nelfinavir,
2 which many of my colleagues is drug number one in
3 the PI. I couldn't find any data, but I would go
4 to a different interaction that might be of
5 importance is drugs which are excreted by the
6 kidney, that might have an effect.

7 DR. STRUBLE: Those are planned, too.

8 DR. YOGEV: Aminoglycosides, probenecid,
9 this type of drug which have an effect, might have
10 a cumulative effect. As for study, just because I
11 didn't mention before, I would like to see them
12 going less than six months of age in the pediatric,
13 and I was negatively impressed, as Dr. Kumar was,
14 about how few women are there, and I think we see
15 more and more data that women are not--so, we need
16 data on women studies for them, and work on them.

17 One other interesting point, I was
18 impressed that in dendritic cells, supposedly the
19 drug was the most active, and this is the beginning
20 of the infection. That is what we are believing
21 now, that it start with dendritic cells, and the
22 long half-life suggested this drug. AZT, by
23 itself, is not as active as tenofovir by itself.
24 It is a monotherapy.

25 So, one other study which might be

1 considered is a perinatal study for transmission,
2 that might be because of the lack of toxicity, and
3 more important is the lack of development of
4 resistance. Nevirapine is already running into
5 trouble because so quickly resistance was found.

6 AZT, we are seeing more and more now
7 transmitted or resistant. Here is a drug that is
8 very difficult to develop resistance, it looks
9 like, and have all the positivity that might have a
10 very good impact on this type of study that I would
11 love to see.

12 DR. GULICK: Dr. Johnson.

13 DR. JOHNSON: At least in our clinic, a
14 lot of HIV HCV coinfecting patients are needing
15 interferon alpha, ribivirin, and ribivirin is
16 renally excreted, and that gets to be a question,
17 especially is they are on 3TC and now you are going
18 to put them on tenofovir.

19 DR. GULICK: Dr. Englund.

20 DR. ENGLUND: I think that a big
21 population for this drug is going to be those
22 patients who are failing all kinds of therapy, and
23 we really need to assess Bactrim and Azithro.
24 Those patient are on routinely the day it is
25 licensed, they are going to be on those, and we

1 don't know any of the interactions. That was
2 number one.

3 Number two, I am concerned about hepatitis
4 B, those of our patients that do have high levels,
5 and I think I would encourage the company to at
6 least be evaluating what is going on with the
7 hepatitis B genotyping and quantitation in patients
8 that are on study. I think that that is a matter
9 of interest, and you wouldn't want to ignore that.

10 Number three, I think we need to also
11 really access this drug in the studies to women of
12 color and minority women, which is where the
13 outbreak is affecting them the most, and women are
14 underrepresented in these trials, but certainly our
15 minority women are heavily underrepresented.

16 DR. GULICK: Dr. Johnson, a follow up?

17 DR. JOHNSON: Yes, just on the comment,
18 too, and support of Gilead, has worked closely with
19 the adult ACTG, protocol A5127, that will compare
20 tenofovir versus adefovir for treatment of
21 coinfectd HIV HBV infected patients failing 3TC to
22 get to one of the community comments earlier.
23 There will be intensive HIV and HBV resistance
24 longitudinal analysis planned in that study.

25 DR. GULICK: Dr. Tebas and then Dr.

1 Hamilton.

2 DR. TEBAS: As a clinician, if it works
3 well in 903, I would like to see studies looking at
4 one of the combinations, because I think it is
5 probably where it is going to be used in the
6 future, and another area that I think potentially
7 has a good market is for post-exposure prophylaxis.
8 The tolerability of the drugs that we use versus
9 post-exposure prophylaxis like nelfinavir is poor.
10 I realize that it is going to be very difficult to
11 show efficacy, but if this drug is a part of the
12 nucleoside regimen, it is better tolerated. It
13 looks like it is not very toxic and is for a short
14 period of time, and most people stop immediately
15 afterwards, that might be potentially an indication
16 for this drug, if it is better tolerated than the
17 currently off-label drugs.

18 Almost half of the people that start
19 post-exposure prophylaxis in the hospital, they
20 stop the drugs because of side effects, and this
21 could be potentially a place that it can be used.

22 DR. GULICK: Dr. Hamilton and then Dr.
23 Munk.

24 DR. HAMILTON: Given the sponsor's
25 intention to rollover 901, 902, and 907 into 910,

1 with the proposed follow up of up to four years, I
2 would encourage them to collect clinical endpoints
3 for later analysis relative to whatever has gone on
4 with respect to surrogate markers, resistance,
5 whatever.

6 In addition, the appearance within the
7 last month of these provocative reports in the New
8 England Journal that indicate GB virus C having an
9 effect on longevity, is bothersome at the very
10 least, but may be an opportunity to look at, if
11 that is real, whether there may be some earlier
12 confounding effect.

13 DR. GULICK: Dr. Munk.

14 DR. MUNK: Yes. Could I ask the sponsor
15 just to remind me, in 903, what is the baseline
16 viral load?

17 DR. TOOLE: The mean baseline viral load
18 in 903 is around 75,000.

19 DR. MUNK: Is it stratified at any point
20 by viral load? It is stratified at over and under
21 100,000? Thank you.

22 DR. GULICK: Other comments from the
23 committee?

24 Let's summarize this point. We have
25 really been thinking about Phase IV commitments all

1 day with some of the issues that we have covered.
2 The committee is in agreement that long-term safety
3 is critical here, both for bone, renal, and other
4 potential toxicities.

5 Measures of efficacy, particularly the CD4
6 responses, given some of the conflicting
7 information we saw today, mutations, that is
8 resistance, mutations over time, and Dr. Hamilton
9 threw in at the last minute clinical endpoints are
10 worth assessing in a four-year long clinical study.

11 We have a number of other populations that
12 we would like to see data in - children less than
13 six months of age. Many times the point was made
14 that in the initial studies, women were
15 underrepresented, particularly women of color on
16 those studies.

17 Other groups that were suggested over the
18 course of the day, those with baseline renal
19 insufficiency, those with baseline hepatic
20 insufficiency, those with concomitant, either
21 hepatitis B infection because of the drug's
22 activity against hepatitis B, and/or hepatitis C
23 activity, either treated or not treated. Those
24 with baseline bone disease or those who developed
25 bone disease from other HIV drugs or the disease

1 itself.

2 Other potential groups to look at,
3 pregnant women, the setting of perinatal
4 transmission, the setting of post-exposure
5 prophylaxis, and the once-a-day setting or perhaps
6 even DOT with antiretrovirals.

7 How is that for a short list to look at?

8 Drug interactions was one area that the
9 committee felt pretty strongly about, even though
10 Dr. Fletcher isn't here, and we will tell him that
11 he was remembered fondly.

12 Some of the drugs that we felt important
13 in terms of antiretrovirals, nevirapine, in terms
14 of the protease inhibitors ritonavir at a dose of
15 at least 400, saquinavir, nelfinavir were all
16 pointed out. Importantly, OI prophylaxes, which
17 will be commonly used in this population, Bactrim
18 and azithromycin being two of the more common, and
19 then renally excreted drugs, such as the
20 aminoglycosides and probenecid.

21 There was some question about dose
22 selection based on the early Phase I studies.

23 I think that is it. From the Agency?

24 DR. STRUBLE: I would like to thank
25 everyone for their comments. I think we got a lot

1 of useful information to help us write an
2 indication in the micro section of the label. We
3 appreciate that.

4 DR. GULICK: I would like to take this
5 opportunity to thank the committee for a very
6 thoughtful and patient day. I would like to thank
7 the sponsor for grace under fire or under rain, as
8 we say, thank the Agency for allowing the day to go
9 so smoothly, and thanks to the audience, too.

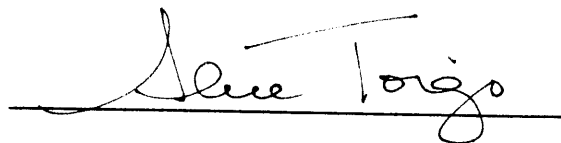
10 [Whereupon, at 4:58 p.m., the proceedings
11 adjourned.]

12

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C E R T I F I C A T E

I, ALICE TOIGO, the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

A handwritten signature in cursive script, reading "Alice Toigo", is written over a horizontal line.

ALICE TOIGO

Lawyer's Notes

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